9:371-386, 1970), λ_n is given by:

$$\lambda_n = \frac{16C}{\sqrt{2}}\left[\frac{1}{\mathrm{Re}_1}\frac{D_1}{D_n}\frac{L_n}{D_n}\right]^{1/2} \qquad (12)$$

where Re_1 is the Reynolds number of the parent branch, C is a constant, D_1 and D_n are the diameters for the parent branch and nth daughter branch respectively, and L_n is the entrance length for the nth daughter branch.

Values of the kinetic energy and dissipation factors are dependent on the nature of flow at the bifurcation. These loss coefficients are approximated by Wolf (Wolf, T. "An Experimental/Theoretical Investigation of Parallel Inhomogeneities in Respiratory Flows." Ph.D. thesis, Dept. of Mechanical Engineering, Massachusetts Institute of Technology: June, 1990; incorporated herein by reference) as:

$$k_n = \left(1 - \frac{1}{K_{c,n}}\right)^2 \quad \text{and} \quad f_n = \left(\frac{1}{K_{c,n}}\right)^2 \qquad (13), (14)$$

The contraction coefficient $K_{c,n}$ represents the ratio between the minimum normal cross-sectional area of the streamtube within the separated region of the nth daughter branch, and the area of the branch itself. Hence, for smaller angles between adjacent daughter branches, separation does not occur and $K_{c,n}$ should approach unity. Using literature values for the anatomical branching angles of the arterial system, a linear relationship between angle and $K_{c,n}$ is assumed and values assigned for each branch. The method is imprecise, however a sensitivity analysis of the contraction coefficients demonstrates that exact values are not required due to their small effect on the system as a whole. The energy conservation equation [Eq. (10)], and the unsteady form of continuity [Eq. (11)] are solved by the MacCormack predictor-corrector computational scheme(Amsterdam, E.A., Banas, J., Cartley, J.M., et al. Clinical assessment of external pressure circulatory assistance in acute myocardial infarction. *Am. J. Cardiol.*, 45:349,

1990; incorporated herein by reference), coupling the state variables of the bifurcation end-nodes with the internal points of the involved arterial elements.

Ventricle. A model of the left ventricle acts as an upstream boundary for the arterial tree. The ventricle may be approximated as a chamber whose compliance (or the inverse of elastance) changes with time, thus driving flow through a unidirectional exit valve into the aorta. Following the work of Suga and Sagawa (Suga, H. and Sagawa, K. Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. *Circulation Research*, 35, 1974; incorporated herein by reference), the specified elastance curve $E(t)$ is used to characterize ventricular ejection and filling. Extensive studies of the pressure-volume relationship in canine ventricles (Suga, H. and Sagawa, K. Instantaneous pressure-volume relationships and their ratio in the excised, supported canine left ventricle. *Circulation Research*, 35, 1974; incorporated herein by reference) have shown that the basic shape of the systolic portion of the pressure-volume curve remains unchanged, regardless of loading or wall compliance changes. Thus, the systolic wall elastance may be characterized by only two parameters; the peak wall elastance, E_{max}, and time to this peak elastance during one cycle, T_{max}. The duration of the cycle is extrapolated from Suga and Sagawa's data suggesting that T_{max} spans approximately 30 - 50% of the total cycle.

In a later extension of this model by Suga and Sagawa (Suga, H., Sagawa, K., Demer, L. Determinants of Instantaneous Pressure in Canine Left Ventricle: Time and Volume Specification. *Circ. Res.* 46: 256-263, 1980; incorporated herein by reference), the effects of myocardial viscoelasticity were taken into account by the addition of one term to the ventricular pressure-volume relation. We found this approach to better fit data for humans (Ozawa, E.T. "A

numerical model of the cardiovascular system for clinical assessment of the hemodynamic state." Thesis, Ph.D., Massachusetts Institute of Technology, September, 1996; incorporated herein by reference) and have consequently used the following form in the present simulations:

$$P_{vent} = E^{*}(t) \cdot \left(V_{vent} - V_{vent,0}\right) \cdot \left[1 + \sigma\left(\frac{dV_{vent}}{dt}\right)\right] + P_{tp} \qquad (15)$$

The coefficient σ is a scaling factor for the time-dependent viscoelastic effects, P_{vent} is the ventricular volume, V_{vent} is ventricular volume, $V_{vent,o}$ is the zero-pressure filling volume, and P_{tp} is the transpulmonary pressure in the chest cavity which is expected to alter the left ventricular transmural pressure. We define the isovolumetric contraction curve $E^{*}(t)$ and assume it to be a half sinusoid, whose duration and amplitude can be modified to represent different compliances and heart rates. Thus, the ventricular pressure may be solved for, given that the flowrate at the root of the aorta is equal to the time derivative of ventricular volume.

Sinuses of Valsalva. As flow begins to reverse, the valve leaflets are swept backwards and close without sustaining a significant pressure gradient. Filling of the sinuses continues until the valve leaflets are maximally distended, at which time the leaflets are able to sustain a pressure gradient. This may be modeled as an abrupt decrease in the aortic root compliance to a new value, C_{sinus}, as well as imposing a zero-flow boundary condition at the first node. This condition is held until the ventricular pressure again exceeds aortic pressure.

Terminal branch points. The numerical model described here uses linear segments to represent the larger vessels in the main arterial tree, but modeling the finer branching structure

approaching the arterioles in this manner is impractical. Rather, the terminal vessels are modeled as a lumped parameter Windkessel (Berger, D.S., Li, J.K-J, and Noordergraf, A. Arterial Wave Propagation Phenomena, Ventricular Work, and Power Dissipation. *Ann. Biome.l Eng.* 23:804-811, 1995; Berger, D.S., Li, J.K-J, and Noordergraf, A. Differential effects of wave reflections and peripheral resistance on aortic blood pressure: a model-based study. *Am. J. Physiol.* 266: *(Heart Circ. Physiol.)* 35:H1626-H1642, 1994; each of which is incorporated herein by reference). The model allows the behavior of the small arterial vessel beds to be captured using only a few parameters and accurately mimics peripheral wave reflections (Ozawa, E.T. "A numerical model of the cardiovascular system for clinical assessment of the hemodynamic state." Thesis, Ph.D., Massachusetts Institute of Technology, September, 1996; incorporated herein by reference). The Windkessel consists of a resistance R_s in parallel with a compliance C_s, where the resistance represents the pressure drop associated with the terminal arterioles, and the compliance represents the total compliance of the small artery network. In series upstream from the Windkessel is an additional element Z_o, which represents the entrance impedance of the small arterial bed with an associated pressure drop of $P - P_c$, where P is the pressure at the last node in the terminating arterial segment, and P_c is the capillary bed pressure. This impedance is matched to that of the adjoining element to avoid the generation of reflections resulting from an impedance mismatch at this interface. Thus, Z_o is approximated as $\rho c / A$ using the wavespeed and area for the element node bordering the Windkessel. From the electrical analogue, the following equations may be written as a function of the resistances and capacitances:

$$\frac{P_c - P_v}{R_s} + C_s \frac{dP_{tm}}{dt} = Q \qquad (16)$$

$$Q = \frac{1}{Z_o}(P - P_c) \qquad (17)$$

where Q is flow entering the Windkessel, P_v is the venous pressure, and $P_{tm} = P_c - P_e$ is the transmural pressure, where the external pressure P_e may be specified. The Windkessel is coupled numerically to its upstream element in this model using the method of characteristics.

Within the region of external compression the externally applied pressure is used as the reference pressure for the capacitor in the windkessel model. Venous pressure is assumed constant for the purpose of these calculations. Consequently, the dynamics occurring on the venous side of the circulation, while potentially important, are not considered in the present calculations. The implications of this assumption are discussed later.

The model, as implemented for these simulations, is operated in "open mode" in that the venous and pulmonary circulations have been omitted. In so doing, the dynamics of the venous bed associated with EECP are essentially ignored on the assumption that the changes in mean venous pressure due to EECP will have minimal effect on the *pulsatile* flows and pressures on the arterial side. Variations of venous pressure in the region of compression may have a somewhat greater effect as discussed below.

Parameter Specification. Information on cardiovascular system parameters exists, but the data are highly variable and extremely dependent on the state (*e.g.* posture) of the individual or animal at the time when measurements are taken. Nonetheless, a standard case that produces a reasonable model output for a given set of parameters is required. Avolio (Avolio, A.P. Multi-branched model of the human arterial system. *Med. Biol. Eng. Comput.* 18:709-18, 1980; incorporated herein by reference) presents an extensive list of arterial lengths, diameters, wall

thicknesses, and Young's moduli for most of the major human arteries (a sum total of 128). For the present model, 30 elements are used. This network is shown schematically in Fig. 1. The numbered elements correspond to major arteries whose properties are provided in Table 2.

Table 2. Specifications for the 30 element model: arterial properties. Proximal and distal cross-sectional areas are given, and it is assumed that area varies linearly with distance along the vessel. E is the Young's modulus of the vessel wall.

element #	artery name	length (m)	proximal area ($x10^{-4}m^2$)	distal area ($x10^{-4}m^2$)	E x 10^5 (Pa)
1	ascending aorta	0.055	6.605	3.941	4.0
2	aortic arch	0.02	3.90	3.90	4.0
3	aortic arch	0.02	3.80	3.80	4.0
4	thoracic aorta	0.185	3.597	2.835	4.0
5	abdominal aorta	0.043	2.378	2.378	4.0
6	abdominal aorta	0.096	1.021	1.021	4.0
7	common iliac	0.192	0.849	0.229	4.0
8	femoral artery	0.432	0.181	0.126	8.0
9	anterior tibial artery	0.015	0.053	0.053	16.0
10	brachiocephalic	0.024	1.208	1.208	4.0
11	r brachial	0.410	0.503	0.181	4.0
12	r common carotid	0.168	0.503	0.503	4.0
13	l common carotid	0.110	0.503	0.503	4.0
14	l brachial	0.444	0.554	0.181	4.0
15	r radial	0.229	0.08	0.08	8.0
16	r ulnar	0.232	0.139	0.113	8.0
17	r external carotid	0.113	0.196	0.071	8.0
18	r internal carotid	0.172	0.283	0.053	8.0
19	l internal carotid	0.172	0.283	0.053	8.0
20	l external carotid	0.113	0.196	0.071	8.0
21	l radial	0.229	0.08	0.08	8.0
22	l ulnar	0.232	0.139	0.113	8.0
23	coeliac	0.010	0.478	0.478	4.0
24	renal	0.027	0.212	0.212	4.0
25	sup mesenteric	0.054	0.581	0.581	4.0
26	inf mesenteric	0.045	0.08	0.08	4.0
27	profundis	0.121	0.166	0.166	16.0
28	post tibial	0.306	0.102	0.102	16.0
29	ant tibial	0.295	0.031	0.031	16.0
30	peroneal	0.313	0.053	0.053	16.0

Arterial elements were specified in the model by a proximal and distal internal radius, from which the cross-sectional areas were calculated. The area was assumed to be a linear function of length between bifurcations. All elements were discretized into nodes, separated by a spatial increment, nominally 0.01 m. The branching pattern of the arteries was also taken from the arterial tree layout given by Avolio (Avolio, A.P. Multi-branched model of the human arterial system. *Med. Biol. Eng. Comput.* 18:709-18, 1980; incorporated herein by reference). In addition to geometrical measurements, the elasticity of each artery segment is specified in order to calculate the nominal reference wavespeed c_0 for each element, using the Moens-Korteweg equation:

$$c_0 = \sqrt{\frac{Eh}{2\rho R}} \qquad (18)$$

Here, c_0 depends locally upon Young's modulus E, inner radius R, fluid density ρ and wall thickness h. Both R and h were assumed known with the internal static reference pressure P_0 equal to 100 mm Hg (13.3 kPa). Assuming a linear relationship between wall thickness and vessel radius, the model calculates c_0 at each node given dimensions and material properties. Values for Young's modulus (Table 2) were also obtained from Avolio's original data.

Local regulation of flow is extremely transient and dependent on a variety of factors, complicating the task of defining a "standard" distribution of flow. An alternative approach used in this model is based on the observation that the caliber of a vessel is related to the flow rate it conveys. This was first proposed by Murray in 1926 and later shown to result from biological factors that tend to maintain a constant wall shear stress in all arteries (Kamiya, A., Bukhari, R.,

and Togawa, T. Adaptive regulation of wall shear stress optimizing vascular tree function. *Bull. Math. Biol.* 46: 127-137, 1984; incorporated herein by reference). Thus, assuming a blood viscosity of 4.0×10^{-5} kg m^{-1} s^{-1}, and a mean wall shear stress of 1.5 N m^{-2} at a mean arterial pressure of 13.3 kPa (100 mm Hg), the required flow can be calculated for each node within the network. The difference in flow between nodes is assumed due Eq. (4). From the calculated required flow at each distal boundary node, the appropriate value of the terminal Windkessel resistance R_s is determined for each terminal element. This method provides values of mean flowrate that are in reasonable agreement with known physiological values. Where the predicted values differ from literature values, adjustments have been made. Values of other hemodynamic parameters are shown in Table 3.

Table 3. External Pressurization Input Control Parameters. All times referenced to the beginning of cardiac systole.

Parameter	Description	Baseline Values
T_{infl}	Time from onset of cardiac cycle at which pressure starts to rise	0.20 s
T_{defl}	Time to begin deflation of cuffs from maximum external pressure	0.72 s
T_{card}	Period of cardiac cycle	0.86 s
P_{calf}	Maximum external pressure applied to calf vessels	200 mmHg
P_{th}	Maximum external pressure applied to thigh vessels	150 mmHg
P_{la}	Maximum external pressure applied to lower abdomen vessels	100 mmHg
Δt_{seg}	Time interval between inflations of adjacent cuff regions with the proximal region always pressurized first	0.03 s
t_{ramp}	Time it takes pressure to rise to and fall from its maximum value	0.03 s
ΔP_{seg}	Pressure difference between cuffs (pressure always increasing in the direction of the foot)	50 mmHg
P_m	Average applied pressure in the three cuff regions	150 mmHg

A base state was chosen, typical of conditions used clinically, from which the effects of various parameter variations could be studied. All data presented are taken from the tenth heart cycle of the model to ensure that the simulation has reached a steady state. A heart rate of 72 beats/min is used for all simulations. Values of the control parameters used for this base state are given in Table 3. Some judgment was exercised in parameter selection. A second set of parameter values, with peak ventricular contractility reduced from 6000 to 1000 dyn/cm^5, systemic vascular resistance increased from 1000 to 2666 dyn/cm^5 and end diastolic volume increased from 120 to 280 ml was used to simulate a patient with compromised ventricular function. Validation of the model with normal parameters included comparisons to measured waveforms at various locations in the arterial system and measured arterial input impedance. Comparisons were also made to pressure and velocity traces found in the literature, but since these vary considerably among individuals direct comparisons are of limited value. These can be found in Ozawa (Ozawa, E.T. "A numerical model of the cardiovascular system for clinical assessment of the hemodynamic state." Thesis, Ph.D., Massachusetts Institute of Technology, September, 1996; incorporated herein by reference).

External Pressurization Scheme. A three-step *graded-sequential* compression procedure was employed in all the simulations presented here. In sequential compression, a wave of compression is applied to the vessels by inflating the three pressurization cuffs for the calves, thighs, and lower abdomen sequentially from ankle to groin. The pressure level applied by the cuffs decreases from calf to thigh, and from thigh to lower abdomen cuffs. In contrast to the emptying behavior characteristic of uniform compression, *sequential compression* produces a

collapse in the vessels that proceeds from the foot toward the heart. Thus, the blood is effectively "milked" from the vessels in the lower extremities and does not pass through a constrictive throat as in uniform compression (Lueptow, R.M., Karlen, J.M., Kamm, R.D., Shapiro, A.H. Circulatory Model Studies of External Cardiac Assist by Counterpulsation. *Cardiovascular Research*, 15(8):443-455, 1981; incorporated herein by reference). In *graded compression* the maximum level of pressure attained in each segment is greatest in the periphery and falls in the direction of the heart. The application of graded compression also helps to eliminate the occlusive throat and, in combination with sequential pressure application, produces rapid and complete emptying of the vessels (Lueptow, R.M., Karlen, J.M., Kamm, R.D., Shapiro, A.H. Circulatory Model Studies of External Cardiac Assist by Counterpulsation. *Cardiovascular Research*, 15(8):443-455, 1981; Zheng, Z.S., Li, T.M., Kambic H., *et al.* Sequential external counterpulsation (SECP) in China. *Transactions of the American Society of Artificial Internal Organs*, 29:599-603, 1983; each of which is incorporated herein by reference).

The cuffs used to provide pressurization of the lower extremities in EECP are modeled as external pressure sources on the lower abdomen, thigh, and calf arteries. To simulate graded-sequential compression in the model, the arterial tree elements for the lower body are divided into three regions, shown in Fig. 1, representing the areas covered by the three pressurization cuffs in EECP.

External Pressurization Control Parameters. Clinical and computational studies have shown the efficacy of EECP depends upon the mode of operation and parameter values used to control the device (Bai, J., Wu, D., Zhang, J. A Simulation Study of External Counterpulsation. *Comput. Biol. Med.*,. 24(2):145-156, 1994; incorporated herein by reference). These parameters include

the cuff inflation and deflation timings, the maximum pressure level applied externally to the vessels by each cuff, and the time delay of pressurization and depressurization between the calf, thigh, and lower abdomen cuffs for sequential compression. Table 3 shows a detailed description of the individual input control parameters governing external pressurization in the model.

In clinical practice, the application of external pressure during EECP is timed with the patient's electrocardiogram. In the EECP model, this process is accomplished by adjusting the timing of applied external pressure in each of the three compartments relative to left ventricular contraction, as characterized by E(t). For graded-sequential compression, the pressure in each cuff rises linearly to its maximum value over a time t_{tramp}, is held constant until a time T_{defl}, and then falls linearly over a time t_{ramp}. The calf, thigh, and lower abdomen cuffs are inflated at times T_{infl}, $T_{infl}+\Delta t_{seg}$, and $T_{infl}+2\Delta t_{seg}$, respectively. The maximum applied pressure is decreased between the calf and thigh cuffs and the thigh and lower abdomen cuffs as specified by P_{calf}, P_{th}, and P_{la}. The cuff deflation time, T_{defl}, is the same for all three cuffs to simplify the parameter study. The parameters used in the temporal application of external pressure during the heart cycle are given in Table 3. For all other parameter values, see Ozawa (Ozawa, E.T. "A numerical model of the cardiovascular system for clinical assessment of the hemodynamic state." Thesis, Ph.D., Massachusetts Institute of Technology, September, 1996; incorporated herein by reference).

Mean applied pressure was chosen at a level thought to produce minimum trauma to the patient while still providing a reasonable measure of benefit. The pressure increment between segments was viewed as sufficient to prevent proximal arterial collapse and a consequent impairment of vessel emptying while still providing ample pressure at the lower abdomen region to produce significant emptying. Consistent with the notion that arterial emptying should

proceed at a speed comparable to the speed of the arterial pressure pulse (about 8 m/s in the peripheral arteries), the time delay between segment compressions was chosen to be approximately equal to the wave transit time through each of the pressurized compartments. Pressure rise time, as shown by Bai *et al.*, should be as short as possible (Bai, J., Ying, K., Jaron, D. Cardiovascular responses to external counterpulsation: a computer simulation. *Med. Biol. Eng. Comput.*, 30:317-323, 1992; incorporated herein by reference). Therefore, a value was chosen close to the practical lower limit.

External Pressurization Measures of Merit. The effectiveness of enhanced external counterpulsation is assessed in terms of the following measures of merit:

Mean Diastolic Pressure. The increase in diastolic pressure, or diastolic augmentation, is characterized by the mean diastolic pressure ratio:

$$\boldsymbol{MDP} = \frac{\left[\frac{1}{T_D - T_S}\int_{T_S}^{T_D} P_{aortic}\,dt\right]_{compr} - \left[\frac{1}{T_D - T_S}\int_{T_S}^{T_D} P_{aortic}\,dt\right]_0}{\left[\frac{1}{T_D - T_S}\int_{T_S}^{T_D} P_{aortic}\,dt\right]_0} \qquad (19)$$

where P_{aortic} is pressure at the aortic root, T_D and T_S are the times at which diastole and systole end, and the subscripts "compr" and "0" refer to cases with and without external compression, respectively ***MDP*** is an indication of how diastolic pressure is increased with pressurization. All pressures are measured when the model has reached steady-state after 10 heart cycles.

Mean Systolic Pressure. The effect of EECP on systolic pressure is quantified using the mean systolic pressure ratio:

$$\boldsymbol{MSP} = \frac{\left[\frac{1}{T_S}\int_0^{T_S} P_{aortic}\,dt\right]_0 - \left[\frac{1}{T_S}\int_0^{T_S} P_{aortic}\,dt\right]_{compr}}{\left[\frac{1}{T_S}\int_0^{T_S} P_{aortic}\,dt\right]_0} \qquad (20)$$

MSP is a measure of the extent of left ventricular afterload reduction with pressurization.

Emptying Effectiveness. The blood volume emptied from the leg vessels enters the aorta, and hence determines the amount of diastolic augmentation achieved by EECP. It also provides a measure of the extent to which arterial diameter changes, and therefore relates to vessel wall strain. The emptying effectiveness parameter, ***EE***, is used to measure the efficiency of the emptying process for the vessels receiving pressurization. ***EE*** is calculated for a single vessel using the equation:

$$\boldsymbol{EE} = \frac{\left[\int A \cdot dx\right]_0 - \left[\int A \cdot dx\right]_{compr}}{\left[\int A \cdot dx\right]_0} \qquad (21)$$

where A is the cross-sectional area of the artery. The integrations are taken over the entire region of pressurization for the artery of interest. For the "compr" case, arterial area is measured at maximum pressurization in diastole just prior to cuff deflation. The arterial area for case "0" is measured at the time step just preceding pressurization. Thus, the emptying effectiveness of

the artery represents the extent of arterial collapse under maximum pressurization with respect to the state of the artery just prior to pressurization. The state of the artery prior to pressurization is considered since the artery may be partially collapsed if there has not been sufficient time for it to completely refill.

Shear Stress Index. An approximate measure of shear stress is defined, that accounts for the changes in cross-sectional area and flow velocity that accompany EECP. In the case of steady, fully-developed, laminar flow through a vessel of circular cross-section, wall shear stress could be computed as follows:

$$\tau_w = \mu \frac{4\bar{V}}{\sqrt{A/\pi}} \tag{22}$$

where $\bar{V}$ is the mean flow velocity. Recognizing that as an artery collapses, its cross-section will likely deviate from circular, and that the flow is clearly not fully-developed nor steady, we will still assume to a rough approximation that

$$\tau_w \propto \mu \frac{\bar{V}}{\sqrt{A}} \tag{23}$$

Actual values of shear stress will be larger than this due to the change in vessel shape and unsteadiness. However, as these effects are difficult to estimate accurately without resorting to fully three-dimensional calculations, we have chosen instead to use eq. (23) for the purpose of

estimating the relative values of shear stress between simulations with and without EECP. Accordingly, a shear index, S, is defined as

$$S = \frac{\sum_{n=1}^{3} \bar{\tau}_{w,compr} - \sum_{n=1}^{3} \bar{\tau}_{w,0}}{\sum_{n=1}^{3} \bar{\tau}_{w,0}} \qquad (24)$$

where $\bar{\tau}_{w,compr}$ is the time integral of the wall shear stress for one cycle evaluated at the mid-point of the compression zone and $\bar{\tau}_{w,0}$ is the same value with no external pressurization. The summation sign indicates that the values of $\bar{\tau}_{w,compr}$ and $\bar{\tau}_{w,0}$ are summed over the three compression zones.

Results

Pressure pulses at the radial artery and aortic root computed by the model (Fig. 3) with and without graded-sequential external compression from the lower abdomen to the foot clearly illustrate the hemodynamic effects of EECP. Compression of a "normal" subject (Fig. 3a) is contrasted to EECP in a patient with reduced ventricular function (Fig. 3b). In both cases, pressure is applied by a three-compartment cuff with maximum pressures of 200, 150 and 100 mmHg along the lower leg, upper leg, and lower abdomen, respectively. Note that in this instance of arterial counterpulsation (pressure application during cardiac diastole and release of pressure during systole) systolic pressure is reduced while diastolic pressure is augmented, leading to the combined effects of reduced ventricular afterload and enhanced coronary blood flow.

The effectiveness of EECP can be viewed in terms of the measures of merit defined previously. These results, computed for the "normal" subject, are shown in Table 4. Numbers shown in the table correspond to the fractional change in each measure from the case without compression and are defined so that they range in value from zero (no effect) to order one.

Table 4. Values for each of the measures of merit for the baseline conditions given in Table 3.

	Values under baseline conditions
MDP	0.0782
MSP	0.0238
EE	0.373
S	3.22

For this same condition of external compression, the time-varying arterial cross-sectional area and a measure proportional to the time-varying shear stress (see Eq. (23)) are plotted for three locations (lower abdomen, thigh, and calf) in Figs. 4 and 5. During pressure application, the arteries collapse with sufficient speed to cause a flow reversal throughout much of the arterial network and a significant increase in vascular shear stress in the arteries of the lower extremity. The arteries in the lower abdomen and thigh (Figs. 4(a) and 4(b), respectively) refill rapidly upon pressure release, even rising to slightly above normal levels due to the strong compression wave generated and its reflection from the peripheral vascular bed. During refilling, shear stress attains levels roughly 3- to 4-fold higher than under normal conditions at all three locations (Fig. 5). Features of particular interest in the context of endothelial function are the high shear stresses of reversing sign, and the significant arterial wall strain due to arterial collapse.

One way to elucidate the relative effects of the various compression parameters is by the sensitivity matrix of Table 5.

Table 5. Sensitivity matrix. Each numerical value represents the fractional change in the particular measure of merit [$\Delta(MM)/MM_{mean}$] divided by the fractional change in the parameter [$\Delta Y/Y_{mean}$] as defined in Eq. (25). Note that a positive value indicates an increase in magnitude of the measure of merit for a positive change in the parameter.

Y =	P_m	ΔP_{seg}	t_{ramp}	Δt_{seg}	T_{infl}
MDP	1.01	-0.140	-0.107	-0.086	-0.887
MSP	1.26	-0.512	-0.147	0.067	-0.059
EE	-0.614	0.236	-0.075	-0.029	0.702
S	2.82	-0.193	-0.028	0.107	0.616

Considering that each measure of merit (***MM***) (e.g., mean diastolic pressure, ***MDP***) is a function of each of the adjustable parameters (Y) (e.g., mean applied pressure), then an entry in the table (X) represents the change in the measure of merit [$\Delta(MM)$] divided by the fractional change in the parameter value:

$$X = \frac{[\Delta(MM) / MM_{mean}]}{[\Delta Y / Y_{mean}]} \qquad (25)$$

Large values indicate strong correlations between the measure of merit and the particular parameter. For example, a 10% increase in mean applied pressure (P_m) will produce an increase of 0.0078 (= 0.1 ·1.01 ¨0.0782) in ***MDP***. This table is useful for identifying the parameters that, when varied, will have the greatest influence on the measure of interest.

While the dependencies are generally quite symmetric about the baseline case suggesting a nearly linear dependence, there is one notable exception. The time to initiate cuff inflation

(T_{infl}) selected for the baseline case was near the optimum in terms of reducing mean systolic pressure. Thus, although T_{infl} has a strong influence on most of the measures of merit, increasing or decreasing it by small amounts from the baseline case does not appear to have much effect on ***MSP***. Changes of larger magnitude, however, will have significant deliterious effects; *e.g.*, if cuff inflation occurs earlier, before the end of systole, systolic unloading will be severely affected.

Mean applied pressure clearly has the greatest potential to enhance diastolic pressure and increase levels of shear stress, although increasing mean pressure probably has the largest *negative* impact on patient tolerance. Altering cuff inflation time also exerts an important influence, although some of its effects are counter-productive (*e.g.*, when ***S*** and ***EE*** increase, ***MDP*** falls). Reducing pressure rise time (t_{ramp}) is also beneficial, although this may be difficult to accomplish in practice.

Discussion

The simulations of EECP presented here, provide insight into the dynamic processes that accompany EECP. Beginning near the end of systole, compression produces arterial collapse, sending a wave of retrograde flow up into the aorta, increasing pressure up as far as the aortic root and, presumably, augmenting coronary blood flow. When compression is released near the end of diastole, the arteries begin to refill, initiating a rarefaction wave that propagates toward the heart, reaching it at a time that produces systolic unloading. The extent of emptying of the leg arteries decreases toward the periphery, but corresponds to approximately half their normal arterial volume within the range of pressures tested here. Refilling to normal volumes is achieved in the most proximal arteries, but even at the levels of pressure used in these

simulations, is incomplete in the lower leg. Increasing pressure applied to the calf up to 300 mmHg (results not shown) compromises refilling even further. The results in Table 3 demonstrate the potential for controlling mechanical events related to cardiac assist or vascular cell stimulation, and perhaps more importantly, show that optimization of the measures relating to cardiac function is not always consistent with optimization of the vascular stimulus.

In previous models of EECP, the arteries were represented as a collection of lumped elements and were therefore not capable of accurately capturing many of the phenomena associated with wave propagation through the arterial network and arterial collapse (Bai, J., Wu, D., Zhang, J. A Simulation Study of External Counterpulsation. *Comput. Biol. Med.*,. 24(2):145-156, 1994; Bai, J., Ying, K., Jaron, D. Cardiovascular responses to external counterpulsation: a computer simulation. *Med. Biol. Eng. Comput.*, 30:317-323, 1992; each of which is incorporated herein by reference). The present model, though still discretized, solves the distributed differential equations and also incorporates the nonlinearities associated with arterial collapse and convective acceleration which are critical under conditions of EECP. Consequently, the model captures the influence of forward and backward propagating waves, can reproduce the complex impedance of real arterial networks (Ozawa, E.T. "A numerical model of the cardiovascular system for clinical assessment of the hemodynamic state." Thesis, Ph.D., Massachusetts Institute of Technology, September, 1996; incorporated herein by reference), and thereby provides a means to examine the detailed flow dynamics associated with EECP. As seen in Fig. 4, the onset of compression at the lower leg sends a surge of blood toward the heart, producing the rapid rise in cross-sectional area in the thigh (see *e.g.*, t=3.60 s in Fig. 4(b)) and the lower abdomen (t=3.64 s in Fig. 4(a)) just prior to compression of these regions. The abrupt fall in cross-sectional area in the calf (beginning at t=3.56 s, Fig. 4(c)) is followed by an equally

abrupt rise in area, before the area decreases more consistently as pressure is maintained. The low frequency oscillation occurring in the iliac artery (t=2.9-3.2 s, Fig. 4(a)) is evidence of wave reflection from the proximal end of the aorta, causing some refilling while pressure is still maintained. These waves are highly damped, however, and are not seen in the thigh or calf regions.

These results, in terms of the magnitude of the effect observed in arterial blood flow and pressure, can to some extent be compared with previous observations. In the multi-center study, the hemodynamic effects of EECP were monitored by determining an "effectiveness ratio" defined as peak diastolic pressure minus end-diastolic pressure divided by peak systolic pressure minus end-diastolic pressure (Arora, R.R., Chou, T.M., Jain, D., Fleishman, B., Crawford, L., McKiernan, T., Nesto, R.W. The multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. *J. Am. Col. Cardiol.*, 33(7):1833-1840, 1999; incorporated herein by reference). Using the aortic blood pressure trace, this ratio is 0.90 for our standard case (Fig. 3b) and 1.60 for the case with a compromised ventricle ("diseased") simulation (Fig. 3d) compared to an average of 1.41 ± 0.51 in the multi-center trial. Note that the patient values (1) were based on measurements with a finger plethysmograph and therefore are not directly comparable to our predictions, and (2) were obtained using maximum pressures up to 300 mmHg. In a separate study, most effects (e.g., change in cardiac output, ratio of retrograde to antegrade aortic flow) had nearly reached their maximal effect when the diastolic-to-systolic pressure ratio reached values in the range of one to 2 (Suresh, K., Simandl, S., Lawson, W.E., Hui, J.C., Lillis, O., Burger, L., Guo, T., Cohn, P.F. Maximizing the hemodynamic benefit of enhanced external counterpulsation. *Clinical Cardiology*, 21(9):649-653,1998; incorporated herein by reference).

We chose to study a range of pressures below those currently used clinically in recognition of the relatively high number of adverse experiences reported by patients receiving EECP. In the multi-center study (Arora, R.R., Chou, T.M., Jain, D., Fleishman, B., Crawford, L., McKiernan, T., Nesto, R.W. The multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. *J. Am. Col. Cardiol.*, 33(7):1833-1840, 1999; incorporated herein by reference), 54.9% of patients experienced adverse effects, with the majority of these being device-related. The number of device-related adverse effects was reduced nearly 4-fold (from 37 to 10) in a separate group of patients in whom applied pressures were decreased from 300 mmHg to 75 mmHg. Our results indicate that significant hemodynamic effects, especially in terms of enhancing arterial shear stress and arterial wall strain, can be achieved with the use of considerably lower pressures, with mean values in the range of 150 mmHg.

Our assumption of constant venous pressure has several potential implications. Consider first the effect of compression on the veins of the lower extremity. The magnitude and frequency of compression will almost certainly cause these veins to be in a state of collapse throughout the cycle since venous valves prevent rapid refilling as occurs on the arterial side. Thus, during compression, venous pressure will be at or slightly elevated above central venous pressure, but during the relaxation phase it will be strongly negative. We anticipate that this would lead to an increase in mean limb flow but of unknown magnitude. A second effect of compression, secondary to the collapse of the veins of the lower extremities, would be a slight elevation of central venous pressure leading to enhanced venous return and activation of the atrial baroreceptors. The effects of these changes are difficult to predict with the present model, and deserve further attention. For the purpose of predicting the pulsatile changes in flow and cross-

sectional area in the leg arteries, however, these changes on the venous side should have relatively little impact. Several additional simulations (results not shown) were conducted with end diastolic volume increased by 20 ml, and with venous pressure increased 5 mmHg. The latter produced results indistinguishable from those presented here. The increase in end diastolic volume led to an overall increase in arterial pressure by about 10 mmHg, but the pressure profile with EECP changed very little. The net effect would be a reduction in systolic unloading and an increase in diastolic augmentation.

Another potential source of uncertainty relates to the values for elastic modulus used for the arterial tree. Although we used the only data we were aware of in the literature[3], these are only estimates and are therefore subject to error. Since the stiffness of the arteries under collapse is based on these estimates, it is possible that the pressures required to produce a certain degree of arterial emptying may also be uncertain. Add to this the subject-to-subject variability likely to be present, and it is apparent that these results should be used only as a rough guide to estimating the parameter values for any particular subject, and that some amount of empirical testing is essential in practice.

It is interesting to note that recent clinical results show benefits in cardiac function from as little as one hour of treatment per day. Under this protocol, Lawson *et al.*, found that 17 out of 18 patients receiving EECP for as little as 36 one-hour treatments reported improvement in anginal symptoms, despite prior medical and surgical therapy (Lawson, W.E., Hui, J.C., Soroff H.S., Zheng, Z., et al. Efficacy of enhanced external counterpulsation in the treatment of angina pectoris. *American Journal of Cardiology*, 70(9):859-862, 1992; incorporated herein by reference). The results of the recent multi-center study involving 139 patients confirmed these findings and showed that EECP reduces exercise-induced ischemia and angina (Arora, R.R.,

Chou, T.M., Jain, D., Fleishman, B., Crawford, L., McKiernan, T., Nesto, R.W. The multicenter study of enhanced external counterpulsation (MUST-EECP): effect of EECP on exercise-induced myocardial ischemia and anginal episodes. *J. Am. Col. Cardiol.*, 33(7):1833-1840, 1999; incorporated herein by reference). A 1996 study by Lawson et al. also showed improved exercise tolerance in 22 out of 27 patients with chronic stable angina (Lawson, W.E., Hui, J.C., Zheng, Z.S., Burgen, L., Jiang, L., Lillis, O., Oster, Z., Soroff, H., Cohn, P. Improved exercise tolerance following enhanced external counterpulsation: cardiac or peripheral effect? *Cardiology*,. 87(4):271-275, 1996; incorporated herein by reference).

While the mechanism by which patients accrue benefit from EECP treatments remains unclear, evidence points to the importance of factors other than the obvious mechanical ones that prompted early studies of EECP as an external cardiac assist method. It is now thought that the benefits of EECP may be related to the recruitment of collateral vessels in the coronary circulation, perhaps due to an increase in the synthesis and release of vascular growth factors (Soran, A.U., Crawford, L.E., Schneider, V.M., and Feldman, A.M. Enhanced external counterpulsation in the management of patients with cardiovascular disease. *Clinical Cardiology*, 22(3): 173-178, 1999; incorporated herein by reference).

Recently, Soran *et al.* have proposed that EECP may act by altering endothelial function due to changes in the level of shear stress in the arteries (Soran, A.U., Crawford, L.E., Schneider, V.M., and Feldman, A.M. Enhanced external counterpulsation in the management of patients with cardiovascular disease. *Clinical Cardiology*, 22(3): 173-178, 1999; incorporated herein by reference). Although EECP has been shown to increase the perfusion through the carotid and renal arteries by approximately 20% in one study (Applebaum, R.M., Kasliwal, R., Tunick, P.A., Konecky, N., Katz, E., Trehan, N., Kronzon, I. Sequential external counterpulsation increases

cerebral and renal blood flow. *American Heart Journal*, 133(6):611-615, 1997; incorporated herein by reference), the effects of elevated shear on the synthesis and release of various cytokines and growth factors are clearly not restricted to the coronary vascular bed. Shear stress is elevated throughout much of the arterial system, especially in the arteries of the lower extremities by a combination of flow augmentation and reduced arterial cross-sectional areas, producing levels of shear stress up to more than four times normal values. These high levels of shear occur during both antegrade and retrograde flow (Fig. 5). While potentially damaging to the endothelium, these high shear stresses might also provide benefit by stimulating the release of shear-induced angiogenic factors from the arterial endothelium of the lower extremities. This has not previously been considered and clearly deserves further study.

In terms of designing optimal protocols for EECP, it is critically important to understand the mechanism by which myocardial function is improved. In particular, parameter variations that optimize the traditional measures of merit (reduction in systolic pressure and increase in diastolic pressure) are not always consonant with the desire to maximize the magnitude and spatial extent of changes in arterial shear stress in the lower extremity. These issues will need to be better understood before a rationale design of the EECP protocol is possible.

Other Embodiments

Those of ordinary skill in the art will readily appreciate that the foregoing represents merely certain preferred embodiments of the invention. Various changes and modifications to the procedures and compositions described above can be made without departing from the spirit or scope of the present invention, as set forth in the following claims.